

# THE OVERACTIVE BLADDER: PHARMACOLOGIC BASIS OF DRUG TREATMENT

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## ABSTRACT

**Objectives.** To provide an overview of the basis for drug treatment of the overactive bladder.

**Methods.** Published information is evaluated.

**Results.** The causes of bladder overactivity are not known, but theoretically, increased afferent activity, decreased inhibitory control in the central nervous system (CNS) or peripheral ganglia, and increased sensitivity of the detrusor to efferent stimulation may be involved. Several CNS transmitters can modulate voiding, but few useful drugs with a defined CNS site of action have been developed. Drugs that stimulate  $\gamma$ -aminobutyric acid receptors are used clinically. Potentially, drugs affecting opioid, 5-hydroxytryptamine, norepinephrine, dopamine, and glutamatergic receptors and mechanisms can be developed, but a selective action on the lower urinary tract may be difficult to obtain. Traditionally, drugs used for treatment of bladder overactivity have had a peripheral site of action, mainly efferent neurotransmission or the detrusor itself. Antimuscarinic drugs,  $\beta$ -adrenoceptor agonists,  $\alpha$ -adrenoceptor antagonists, drugs affecting membrane channels, prostaglandin synthetase inhibitors, and several other agents have been used with limited success. New information on the  $\alpha$ -adrenoceptor and muscarinic receptor subtypes in the human detrusor has emerged and may be the basis for the development of new compounds with effects on bladder overactivity. Decreasing afferent activity seems an attractive therapeutic approach, and drugs affecting afferent nerves by causing release of tachykinins, such as capsaicin and analogs, as well as agents blocking tachykinin receptors, may be of therapeutic interest.

**Conclusions.** New drugs, specifically designed for the treatment of bladder overactivity, are desirable. *UROLOGY* 50 (Suppl 6A): 74-84, 1997. © 1997, Elsevier Science Inc. All rights reserved.

To effectively treat the overactive bladder, identification of suitable targets for pharmacologic intervention is a prerequisite. With the present knowledge of the central<sup>1</sup> and peripheral<sup>2</sup> control of micturition, sites and drug mechanisms that can influence bladder function can easily be identified. However, the problem is not only to inhibit bladder contraction, but to eliminate overactivity without disturbing normal micturition. Even if this might be possible, there is also a selectivity problem: how to affect bladder function without interfering with the function in other organ systems. In many cases of urinary incontinence (UI) associated with the overactive detrusor, the clinical therapeutic problem is twofold: urine leakage and lower

urinary tract (LUT) symptoms. Overactive detrusor function may or may not be associated with LUT symptoms or urine leakage, and the relations between these factors are far from clarified.

Below, the pharmacologic basis for some of the current therapeutic alternatives for treatment of bladder overactivity, and possible future developments, are briefly discussed.

## IDENTIFICATION OF DRUG TARGETS

As discussed in detail elsewhere,<sup>1</sup> several reflexes are involved in the storage of urine and in voiding. During storage, at low levels of vesical afferent activity, spinal reflexes are active mediating contraction of urethral sphincter mechanisms through somatic (striated muscle) and sympathetic (smooth muscle) nerves. Sympathetic nerves may also mediate detrusor and ganglionic inhibition. There is no activity in the sacral parasympathetic outflow. Micturition is initiated by distention of the bladder, activating mechanoreceptors in the bladder

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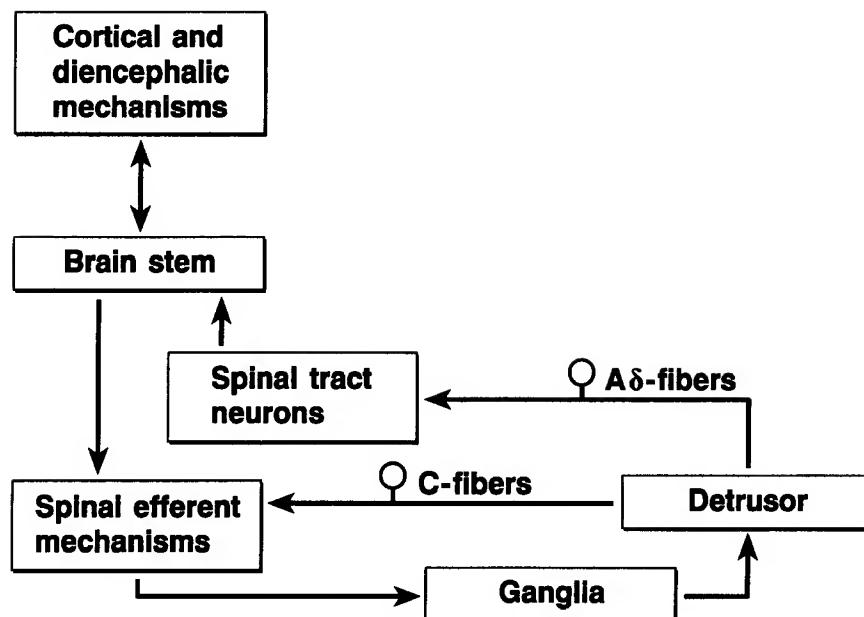


FIGURE 1. *Micturition reflex pathways. Based on de Groat et al.<sup>1</sup>*

wall. This triggers a high level of activity in small myelinated afferent nerves (A $\delta$ ), which via the dorsal root ganglia reaches the lumbosacral spinal cord (Fig. 1).<sup>1</sup> The A $\delta$  afferents connect to a spinobulbospinal reflex consisting of an ascending limb from the lumbosacral spinal cord, an integration center in the rostral brain stem (which is known as the pontine micturition center [PMC]), and a descending limb from the PMC back to the parasympathetic nucleus in the lumbosacral spinal cord. Afferent information may also be conveyed by small unmyelinated (C-fiber) vesical afferents, which have a high mechanical threshold but may be activated by irritation of the bladder mucosa. They may also be active in spinal cord injuries. Efferent micturition reflex pathways reach the bladder through the pelvic nerves.

#### CAUSES OF BLADDER OVERACTIVITY

There is still no consensus about the reasons for developing bladder overactivity. Theoretically, there may be 1) increased afferent activity, 2) decreased inhibitory control in the central nervous system (CNS) or in peripheral ganglia, 3) increased sensitivity to efferent stimulation in the detrusor, or a combination of these factors. Brading and Turner<sup>3</sup> proposed that all cases of detrusor overactivity (idiopathic, neuropathic, and obstructive) have a common feature—a change in the properties of the smooth muscle of the detrusor, predisposing it to unstable contractions—and that this change is caused by a reduction in the functional motor innervation of the bladder wall. They also stressed that bladder instability, as shown in a pig model of obstruction, may occur without partici-

pation of a micturition reflex. It seems difficult, however, to accept that a primary change in the detrusor should be the cause of the bladder overactivity seen in, for example, stroke patients. Even if the pathogenesis of bladder overactivity is unknown (and most probably is different in patients with outflow obstruction, neurogenic bladders, and idiopathic detrusor instability [DI]), drug targets for treatment of UI may be found peripherally or in the CNS.

#### CNS TARGETS

Anatomically, several CNS regions may be involved in micturition control: supraspinal structures, such as the cortex and diencephalon, midbrain, and medulla, and also spinal structures.<sup>1</sup> Several transmitters are involved in the micturition reflex pathways and may be targets for drugs aimed at control of micturition. However, few drugs with a CNS site of action have been developed. Drugs that stimulate  $\gamma$ -aminobutyric acid (GABA) receptors are used clinically. The potent inhibitory effects by opioids are well known, but have not been used therapeutically. Potentially, drugs that affect GABA, opioid, 5-hydroxytryptamine (serotonin), norepinephrine, dopamine, and glutamic acid receptors and mechanisms can be developed, but a selective action on the LUT may be difficult to obtain.

#### GABA

Both GABA<sub>A</sub> and GABA<sub>B</sub> receptor agonists suppress spinal and supraspinal components of the micturition reflex, and there are reasons to believe that in some species the supraspinal micturition

reflex pathway is under a tonic GABA-ergic inhibitory control.<sup>1</sup> The GABA<sub>B</sub> agonist baclofen is considered to depress monosynaptic and polysynaptic motor neurons and interneurons in the spinal cord and has been used in voiding disorders, including detrusor hyperreflexia secondary to lesions of the spinal cord.<sup>4</sup> The drug may also be an alternative in the treatment of idiopathic detrusor overactivity.<sup>5</sup> However, published experience with the drug is limited. Intrathecal baclofen may be useful in patients with spasticity and bladder dysfunction and may increase bladder capacity.<sup>6-8</sup> The therapeutic potential in bladder overactivity of the new generation of antiepileptic drugs, which are able to enhance GABA-ergic transmission by, for example, inhibition of GABA reuptake or GABA-transaminase,<sup>9</sup> would be worth investigating.

#### ENKEPHALINS

Enkephalinergic varicosities are prominent in the regions of the spinal parasympathetic nucleus and the PMC, and enkephalins effectively depress micturition and sphincter reflexes by stimulation of  $\mu$ -,  $\delta$ -, and  $\kappa$ -receptors.<sup>1</sup> It is well established that morphine and other opioids depress micturition, and that this effect can be blocked by naloxone. However, so far drugs with effects on opioid receptors do not seem to have been developed for the treatment of bladder overactivity in humans.

#### SEROTONIN

The lumbosacral sympathetic and parasympathetic autonomic as well as sphincter motor nuclei receive a dense serotonergic input from the raphe-spinal pathway.<sup>1</sup> Drugs interfering with serotonin or with serotonin receptors have not been systematically tested as a treatment of the overactive bladder in humans. Whether or not imipramine, which among other effects blocks the reuptake of serotonin, depresses bladder overactivity by this mechanism,<sup>10</sup> has not been established.

#### NOREPINEPHRINE

Sympathetic, parasympathetic, and somatic nuclei in the lumbosacral spinal cord receive inputs from noradrenergic neurons in the brain stem. Bladder activation through these bulbospinal noradrenergic pathways may involve excitatory  $\alpha_1$ -adrenoceptors.<sup>11</sup> Both in normal rats and in rats with bladder hypertrophy secondary to outflow obstruction undergoing continuous cystometry, doxazosin, given intrathecally, decreased micturition pressure.<sup>12</sup> The effect was much more pronounced in the animals with hypertrophied/overactive bladders. Doxazosin did not markedly affect the frequency or amplitude of the unstable contractions observed in obstructed rats. It was suggested that doxazosin may have an action at the level of the

spinal cord and ganglia, thereby reducing activity in the parasympathetic nerves to the bladder, and that this effect was more pronounced in rats with bladder hypertrophy than in normal rats. Whether or not a spinal/supraspinal site of action contributes to the relief of symptoms, including bladder overactivity, produced by  $\alpha_1$ -adrenoceptor antagonists in patients with benign prostatic hypertrophy (BPH),<sup>13</sup> remains to be established.

#### DOPAMINE

It is well known that patients with Parkinson's disease may have detrusor hyperreflexia, possibly as a consequence of nigrostriatal dopamine depletion and failure to activate inhibitory dopamine D1 receptors.<sup>14</sup> However, other dopaminergic systems may activate D2 receptors, facilitating the micturition reflex. Thus, Sillen *et al.*<sup>15</sup> showed that apomorphine, which activates both D1 and D2 receptors, induced overactivity in anesthetized rats via stimulation of central dopaminergic receptors. The effects were abolished by infracollicular transection of the brain and by prior intraperitoneal administration of the centrally acting dopamine receptor blocker spiroperidol. Kontani *et al.*<sup>16,17</sup> suggested that the bladder overactivity induced by apomorphine in anesthetized rats resulted from synchronous stimulation of the micturition centers in the brain stem and spinal cord, and that the response was elicited by stimulation of both dopamine D1 and D2 receptors. Whether or not drugs that block dopamine receptors can be used for treatment of bladder overactivity has not been established.

#### GLUTAMIC ACID

N-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamatergic receptors seem to play an essential role at excitatory synapses in the descending pathway from the PMC to the spinal parasympathetic nucleus.<sup>11</sup> In adult anesthetized rats, inhibitors of NMDA or AMPA receptors depress the amplitude of reflex bladder contractions and inhibit voiding. In unanesthetized animals, on the other hand, NMDA receptor antagonists decrease the volume threshold for inducing bladder reflex contractions and facilitate micturition. The potential role of drugs acting on glutamatergic receptors for control of bladder overactivity needs further study.

#### PERIPHERAL TARGETS

Anatomically, drug targets for treatment of bladder overactivity may be the bladder, urethra, prostate, ganglia, or peripheral nerves. The mechanisms most often aimed at are receptors or ion

channels known to be involved in the control of bladder contraction, for example, muscarinic receptors and L-type calcium channels. Other mechanisms involved in neurotransmission or in the excitation-contraction coupling of the detrusor smooth muscle may also be targets for pharmacologic interventions.

#### MUSCARINIC RECEPTORS

Antimuscarinic drugs are still the most widely used treatment of urge, sensory, and motor urge incontinence.<sup>4</sup> However, the currently used drugs lack selectivity for the bladder,<sup>18</sup> which limits their usefulness. Theoretically, agents with selectivity for the bladder might be obtained if the subtype(s) mediating bladder contraction, and those producing the main side effects of antimuscarinic drugs, were known.

Several subpopulations of muscarinic receptors have been identified, and at least five different subtypes ( $m_1-m_5$ ) have been cloned. Pharmacologically, four different subtypes ( $M_1-M_4$ ) have been defined,<sup>18</sup> all with a wide distribution in the body. The subtypes that can be demonstrated in the human bladder, and those responsible for bladder contraction, have been studied using various approaches. Cultured human detrusor cells expressed  $M_3$  receptors linked to phosphoinositide hydrolysis,<sup>19</sup> and an important role for  $M_3$  receptors is widely accepted. The  $M_1$ ,  $M_2$ , and  $M_3$  receptor subtypes were demonstrated in human detrusor muscle by receptor binding; there was a distinct predominance of  $M_3$  receptors.<sup>20</sup> However, Yamaguchi *et al.*<sup>21</sup> were able to demonstrate the presence of mRNA encoding the  $m_2$  and  $m_3$  subtypes, but not the  $m_1$ ,  $m_4$ , and  $m_5$  subtypes, in human bladder. Using subtype-specific immunoprecipitation, Wang *et al.*<sup>22</sup> could demonstrate only  $m_2$  and  $m_3$  subtypes in human and rabbit detrusor membranes, the ratio of  $m_2$  to  $m_3$  being 3:1. Despite a predominance of  $m_2$  receptors in rabbit and rat detrusor, several investigators have found that the pharmacologically defined  $M_3$  receptor mediates contraction.<sup>22,23</sup> Recently, however,  $M_2$  receptors were also shown to be able to mediate rat bladder contraction *in vitro* as well as *in vivo* by reversing  $\beta$ -adrenoceptor-mediated relaxation.<sup>24</sup> Future studies with muscarinic receptor antagonists with a selectivity for  $M_3$  receptors, such as darifenacin<sup>25,26</sup> and vamicamide,<sup>27,28</sup> will reveal whether or not the principle of selective  $M_3$  receptor antagonism offers therapeutic advantages. Since  $M_3$  receptors are located not only in the bladder, but also in the salivary glands and the intestine, this could mean that two of the most common side effects, dry mouth and constipation, will not be avoided. However, selective muscarinic receptor antagonists, such as zamifenacin, may be able

to distinguish between  $M_3$  receptors in different smooth muscles.<sup>29</sup> Tolterodine<sup>30</sup> lacks selectivity for muscarinic receptor subtypes, but still shows selectivity for the bladder over the salivary glands in an animal model, and possibly in humans.<sup>31</sup>

Muscarinic receptors, which on stimulation inhibit transmitter release, have been demonstrated on cholinergic nerves in rat bladder.<sup>2</sup> In this organ, three types of cholinergic receptors were demonstrated to affect acetylcholine release.<sup>32,33</sup>  $M_2$  inhibitory receptors dominated in untreated preparations, whereas in physostigmine-treated bladder strips, where the concentrations of acetylcholine were elevated, facilitatory  $M_1$  and nicotinic receptors were also demonstrated. Physostigmine had a biphasic effect, causing inhibition of acetylcholine release at low ( $M_2$ ) and facilitation at high ( $M_1$ ) concentrations. The authors suggested that even if muscarinic inhibitory receptors appear to be the only type activated by acetylcholine released by electrical stimulation under normal conditions, facilitatory receptors may be activated by the high-frequency parasympathetic nerve discharge that occurs during micturition. Particularly in pathologic conditions, such as the neurogenic hyperreflexic bladder, a mechanism like this may contribute to changes in bladder function. Antagonism of  $M_1$  receptors may contribute to bladder inhibition.

Detrusor denervation as a consequence of outflow obstruction has been demonstrated in pigs and humans.<sup>34,35</sup> In detrusor from pigs with experimental outflow obstruction, Sibley<sup>36</sup> found that the response to intramural nerve stimulation was decreased. There was, however, a supersensitivity of the detrusor, including a leftward displacement of the concentration-response curve for acetylcholine. Sibley<sup>36</sup> suggested that this was due to partial denervation of the bladder as a result of the obstruction, and that one consequence of the supersensitivity might be DI. Further supporting the presence of cholinergic denervation in the bladders of obstructed patients with bladder instability, Harrison *et al.*<sup>37</sup> found that in detrusor strips from such patients, the acetylcholine concentration-response curve was significantly shifted to the left, suggesting an increased sensitivity to acetylcholine. On the other hand, Yokoyama *et al.*<sup>38</sup> found that the responses to acetylcholine of detrusor strips from patients with bladder instability were not significantly different from the responses of strips from patients without instability. The reasons for these conflicting results are unclear.

It might be assumed that the muscarinic receptor functions also change in nonobstructed bladders showing overactivity. Kinder and Mundy<sup>39</sup> compared detrusor muscle from human normal, idiopathic unstable, and hyperreflexic (neurological damage) bladders. They found no significant dif-

ferences in the degree of inhibition of electrically induced contractions produced by tetrodotoxin and atropine between detrusor strips from any of these bladders, and no significant differences in the concentration-response curves for acetylcholine. In overactive bladders without associated neurologic disorders, a decreased number of muscarinic receptors has been demonstrated,<sup>40</sup> but its relation to overactivity remains unclear. Isolated detrusor strips from patients with detrusor hyperreflexia were supersensitive to both carbachol and KCl, but responded like normal controls to intramural nerve stimulation. The results were interpreted to suggest a state of postjunctional supersensitivity of the detrusor secondary to a partial parasympathetic denervation of the detrusor.<sup>41</sup>

The muscarinic receptors remain a main target for drugs used to treat the overactive bladder. However, the complexity of muscarinic receptor functions in the bladder and elsewhere in the body makes it difficult to predict the optimal profile of subtype selectivity of antimuscarinic drugs meant for treatment of bladder overactivity.

#### ADRENOCEPTORS

The role of the sympathetic nervous system in human bladder function has been much discussed, partly because of the paucity of the adrenergic innervation of human detrusor muscle. There is no doubt, however, that norepinephrine is released on electrical stimulation of human bladder tissue. In detrusor muscle from several species, including humans,  $\beta$ -adrenoceptors have been shown to dominate over  $\alpha$ -adrenoceptors, and the normal response to released norepinephrine is relaxation.<sup>42,43</sup>

**$\alpha$ -Adrenoceptors.** The predominating postjunctional  $\alpha$ -adrenoceptor subtype in the human LUT seems to be  $\alpha_1$ .<sup>44,45</sup> Recently, Walden *et al.*<sup>45</sup> reported a predominance of  $\alpha_{1a}$ -adrenoceptor protein in the human bladder dome, trigone, and bladder base, but which  $\alpha_1$ -adrenoceptor subtype predominates functionally has not been clarified. Possibly, the  $\alpha_{1L}$ -adrenoceptor subtype is the one mediating contractile responses.<sup>46</sup>

Drugs stimulating  $\alpha$ -adrenoceptors have hardly any contractile effects in isolated, normal human detrusor muscle. However, even if the  $\alpha$ -adrenoceptors have no significant role in normal bladder contraction, there is evidence that this may change in bladder overactivity associated with, for example, outflow obstruction, neurogenic bladders, and idiopathic bladder instability.

Perlberg and Caine<sup>42</sup> found that norepinephrine caused contraction instead of the normal relaxant response in bladder strips from 11 of 47 patients with benign prostatic obstruction. They proposed that there was a correlation between the response

to stimulation on one hand, and bladder instability and irritative symptoms on the other. It has been observed that in patients with BPH treated with  $\alpha$ -adrenoceptor blockers, bladder overactivity (bladder instability) disappears during treatment.<sup>47</sup> Taken together, these observations would suggest that there may be an increased  $\alpha$ -adrenoceptor function associated with the morphologic changes occurring in bladder hypertrophy. On the other hand, Smith and Chapple<sup>48</sup> could not confirm the occurrence of an increased  $\alpha$ -adrenoceptor function in the unstable, obstructed human bladder.

A change in the  $\alpha$ -adrenoceptor function of the detrusor and outflow region associated with outflow obstruction secondary to BPH cannot be excluded. On the other hand, the importance of such a change for the clinical response to  $\alpha$ -adrenoceptor antagonists is difficult to assess. It cannot be excluded that an effect of the  $\alpha$ -adrenoceptor blockers on the CNS contributed to these actions. There are clinical observations in agreement with the view that neurologic damage may be associated with a change in  $\alpha$ -adrenoceptor functions of relevance to detrusor function. In a study of patients with bladder hyperreflexia, Jensen<sup>49</sup> found that treatment with prazosin decreased the overactivity and increased bladder capacity. This was confirmed by other investigators,<sup>50</sup> but the results were not impressive. In children with myelomeningocele and detrusor hyperreflexia, phentolamine injected intramuscularly decreased tone and bladder overactivity.<sup>51</sup> Detrusor tissue from patients with bladder overactivity (without neurologic disorders) had an almost fourfold increase in the density of  $\alpha$ -adrenoceptors compared to the density in patients with normal bladder activity.<sup>40</sup> The importance of this finding for bladder overactivity is, however, unclear.

The  $\alpha_1$ -adrenoceptor subtypes of the LUT and those involved in the central control of the micturition reflexes deserve further attention. Whether or not drugs with a selective effect on  $\alpha_{1L}$ -adrenoceptors can eliminate bladder overactivity should be investigated.

**$\beta$ -Adrenoceptors.** In isolated human bladder, non-subtype-selective and  $\beta$ -adrenoceptor agonists, such as isoprenaline, have a pronounced inhibitory effect.<sup>2</sup> It was speculated that, in bladder overactivity, there is a lack of an inhibitory  $\beta$ -adrenoceptor-mediated norepinephrine response. However, detrusor muscle from patients with bladder instability was reported to show a similar degree of inhibition in response to isoprenaline as normal detrusor,<sup>52</sup> even if the inhibitory effect of isoprenaline on the response to electrical stimulation was less in unstable muscle. However, the  $\beta$ -adrenoceptors of the human bladder were shown

to have functional characteristics typical of neither  $\beta_1$ - nor  $\beta_2$ -adrenoceptors, since they could be blocked by propranolol, but not by practolol or metoprolol ( $\beta_2$ ).<sup>53-55</sup> On the other hand, receptor binding studies using subtype-selective ligands suggested that the  $\beta$ -adrenoceptors of the human detrusor are primarily of the  $\beta_2$  subtype, and favorable effects on bladder overactivity were reported with selective  $\beta_2$ -adrenoceptor agonists, such as terbutaline and clenbuterol.<sup>4,56</sup> Treatment with these agents has been limited by side effects.

Atypical,  $\beta$ -adrenoceptor-mediated responses that were reported repeatedly in early studies of  $\beta$ -adrenoceptor antagonists have recently been shown to be mediated by a  $\beta$ -adrenoceptor that has been cloned, sequenced, expressed in a model system, and extensively characterized functionally.<sup>57,58</sup> Both normal and neurogenic human detrusors were shown to express  $\beta_1$ -,  $\beta_2$ -, and  $\beta_3$ -adrenoceptor mRNA, and CGP-12177A, a  $\beta$ -adrenoceptor partial agonist with  $\beta_1/\beta_2$ -adrenoceptor antagonist activity, effectively relaxed both types of detrusor muscle.<sup>55</sup> Thus, it seems as if the atypical  $\beta$ -adrenoceptor of the human bladder may be the  $\beta_3$ -adrenoceptor.

Experiments in rats<sup>59</sup> have demonstrated an age-related decrease in the responsiveness of the bladder to  $\beta$ -adrenoceptor stimulation, possibly related to a decreased density of  $\beta$ -adrenoceptors and decreased production of cyclic adenosine monophosphate. Whether or not this is of importance in humans and whether  $\beta_3$ -adrenoceptor stimulation will be an effective way of treating the overactive bladder remains to be shown in controlled clinical trials.

#### TACHYKININ AND VANILLOID RECEPTORS

The importance of afferent nerve activity in the pathogenesis of detrusor overactivity has been emphasized by several investigators. Local release of tachykinins (substance P, neurokinin A, neurokinin B) and other peptides from sensory nerves in the bladder wall has been shown to produce diverse biological effects, such as smooth muscle contraction, facilitation of transmitter release from nerves, vasodilatation, and increased plasma permeability.<sup>60</sup> The actions of the tachykinins are mediated by activation of three distinct receptor types termed NK-1, NK-2, and NK-3.<sup>61</sup> Specific tachykinin receptors are present in the smooth muscle of the urinary bladder of several species, including humans. Whereas the rat and guinea-pig detrusors contain both NK-1 and NK-2 receptors, the NK-2 receptor seems to be the only mediator of contractile responses to tachykinins in human bladder smooth muscle.<sup>62-64</sup>

As mentioned previously, the sensation of bladder filling and initiation of the micturition reflex are caused by activation of mechanoreceptors in

the bladder wall, and the responsible afferents are small, slowly conducting myelinated A $\delta$  fibers. Afferents mediating painful sensations are slowly conducting, unmyelinated C-fibers. Experimental studies suggested that the voiding reflex in animals with spinal cord injury is mediated by unmyelinated C-fibers and that this pathway can be blocked by capsaicin.<sup>65</sup> Capsaicin is believed to act on vanilloid receptors,<sup>66</sup> causing desensitization of C-fiber sensory afferents by an initial release and emptying of the stores of neuropeptides and then blocking further release, thereby suppressing sensory neuron activity. Cystometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans was originally presented by Maggi *et al.*,<sup>67</sup> who instilled capsaicin (0.1 to 10  $\mu$ mol/L) intravesically in patients with hypersensitivity disorders. These investigators found a concentration-related reduction of the volume required to elicit the first desire to void, of bladder capacity, and of pressure threshold for micturition, suggesting release of tachykinins. All patients reported disappearance or marked attenuation of their symptoms a few days after administration of capsaicin. Intravesical capsaicin, given in considerably higher concentrations (1 to 2 mmol/L) than those administered by Maggi *et al.*,<sup>67</sup> has since been used with success in patients with bladder overactivity due to neurologic disorders, such as multiple sclerosis or traumatic chronic spinal lesions. The effect of treatment may last for 2 to 7 months.<sup>68-70</sup> These positive effects have been explained by the blocking of C-fiber afferents. It has also been suggested that the ice-water test could be used to determine the dose of capsaicin needed to influence bladder C-fiber afferents adequately.<sup>69</sup>

Resiniferatoxin was shown to be approximately 1,000 times more potent than capsaicin in stimulating bladder activity.<sup>71,72</sup> However, resiniferatoxin was relatively less potent in producing tissue inflammation<sup>71</sup> and seemed to be able to desensitize bladder sensory fibers with less C-fos expression in the rat spinal cord than capsaicin.<sup>73</sup> Resiniferatoxin may therefore be an interesting therapeutic alternative to capsaicin. Supporting this, Lazzeri *et al.*<sup>74</sup> reported that when instilled intravesically in humans (concentration,  $10^{-8}$  mol/L), resiniferatoxin did not produce a warm and burning sensation at the suprapubic/urethral level, an effect that is commonly found with capsaicin. If tachykinins, released from sensory nerves, produce bladder overactivity and hypersensitivity disorders, antagonism of NK-receptors with selective drugs seems to be an interesting, novel way of treating these disorders.

## PROSTANOID

Human bladder mucosa has the ability to synthesize eicosanoids<sup>75</sup> and these agents can be liberated from both bladder muscle and mucosa in response to stimuli, such as stretch of the detrusor smooth muscle, injuries of the vesical mucosa, nerve stimulation, and agents such as adenosine triphosphate (ATP) and mediators of inflammation (see Maggi<sup>76</sup> and Andersson<sup>2</sup>). Even if prostaglandins cause contraction of human bladder muscle, it is still unclear whether they contribute to the pathogenesis of unstable detrusor contractions. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Capsaicin-sensitive afferents in the bladder are chemosensitive and can be activated by prostanoids to increase the afferent input produced by a given degree of bladder filling. Maggi<sup>76</sup> suggested that prostanoids may be the link between detrusor muscle stretch produced by bladder filling and activation of capsaicin-sensitive afferents by bladder distention. Evidence of this was produced in the rat urinary bladder, where intravesical instillation of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) lowered the threshold for reflex micturition, and topical application of PGE<sub>2</sub> and thromboxane B<sub>2</sub> on the serosal surface activated reflex micturition. Both effects were prevented by systemic capsaicin desensitization. Indomethacin pretreatment and systemic capsaicin increased the micturition threshold without affecting the amplitude of the micturition contraction. Since intravesical PGE<sub>2</sub> did not reduce the residual urine volume in capsaicin-pretreated animals, it was suggested that endogenous prostanoids enhance voiding efficiency through an action, direct or indirect, on sensory nerves.<sup>76</sup>

If prostaglandins generated by the bladder increase the afferent input produced by filling, involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be an effective treatment of bladder overactivity. However, clinical evidence for this is scarce. For example, in a double-blind, controlled study of 30 women with DI using the prostaglandin synthesis inhibitor flurbiprofen, the drug was shown to have favorable effects, although it did not completely abolish detrusor overactivity.<sup>77</sup> There was a high incidence of side effects (43%), including nausea, vomiting, headache, and gastrointestinal symptoms. Cyclooxygenase (COX) is the pivotal enzyme in prostaglandin biosynthesis. The constitutive COX-1 is considered responsible for the physiologic functions of the prostaglandins, whereas the inducible COX-2 is involved in inflammation.<sup>78,79</sup> If prosta-

glandins generated by inflammation are contributing to bladder overactivity, it would theoretically be possible to obtain maximal antiinflammatory efficacy combined with less toxicity if the COX-2 was inhibited selectively. Whether or not available selective COX-2 inhibitors would be useful as treatment for bladder overactivity remains to be established.

## ION CHANNELS

*Inhibition of Calcium Influx.* Spontaneous intracellular calcium transients have been demonstrated in isolated human bladder smooth muscle cells,<sup>80</sup> and may be the origin of myogenic activity. However, there are reasons to believe that activation of detrusor muscle, through both cholinergic and nonadrenergic, noncholinergic (NANC) pathways, requires influx of extracellular calcium through dihydropyridine-sensitive calcium channels, as well as mobilization of intracellular calcium.<sup>2</sup> If there is an increased calcium influx in bladder overactivity, one would expect changes in, for example, the binding or functional properties of the voltage-dependent calcium channels. In bladders from children with myelodysplasia, in whom detrusor hyperreflexia is a common phenomenon, this was not found.<sup>81</sup> On the other hand, Saito *et al.*<sup>82</sup> found that the supersensitivity to calcium, demonstrated in rabbit bladder after denervation achieved by bilateral sacral rhizotomy, could be effectively inhibited by a calcium antagonist, and it was hypothesized that a hyperpermeability to calcium was responsible for this phenomenon. If so, this would be in agreement with the finding of an increased sensitivity to depolarizing stimuli in the hypertrophic rat bladder.<sup>83</sup>

Considering the importance of calcium influx for contractile activation, blockade of L-type calcium channels seems to be an attractive way of inhibiting bladder contraction. By voltage clamp, nifedipine was shown to decrease the inward Ca<sup>2+</sup> current in guinea-pig urinary bladder smooth muscle cells.<sup>84</sup> This is in line with the finding that, irrespective of the mode of activation, nifedipine inhibited detrusor contraction in isolated human detrusor preparations.<sup>85</sup> Nifedipine also abolished the NANC-mediated contractile component in rabbit<sup>86</sup> and rat detrusor<sup>87,88</sup> and the atropine-resistant contractile component in hypertrophic human detrusor muscle.<sup>89</sup> Available information suggests that systematic therapy with L-type calcium antagonists is not an effective way to treat detrusor overactivity, but controlled clinical trials are lacking. However, the possibility that intravesical therapy with these drugs will be useful should not be ignored, nor should the fact that calcium antagonists may enhance the effects of anticholinergic agents.<sup>2</sup>

*Potassium Channels.* ATP-mediated transmission

can be demonstrated in the human bladder,<sup>90,91</sup> but normally probably plays a minor functional role. However, this may change in, for example, outflow obstruction, where 25% of the detrusor response to electrical stimulation was found to be NANC,<sup>48</sup> or in the neurogenic bladder, where the NANC component was 40%.<sup>92</sup>

If ATP is of importance for bladder overactivity, it is important to block the activation mechanism for this transmitter. This may be achieved by blockade of bladder  $P_{2X}$ -purinoceptors by suramin<sup>92</sup> or, since ATP-induced activation is dependent on calcium influx,<sup>2</sup> by inhibition of such influx by L-type calcium channel antagonists. Calcium influx inhibition can also be obtained by hyperpolarization of the detrusor muscle cell membrane by the opening of potassium channels.<sup>93</sup> However, potassium channels are known to be ubiquitous and diverse, and lack of selectivity for the bladder versus the vasculature has thus far limited the use of available drugs. In, for example, the guinea-pig detrusor, at least three types of potassium channels have been demonstrated: ATP-sensitive ( $K_{ATP}$ ); small conductance and calcium-dependent ( $SK_{Ca}$ ); and large conductance and calcium-dependent ( $BK_{Ca}$ ). ATP-sensitive potassium channels have been found in human detrusor muscle, and calcium-activated potassium channels ( $BK_{Ca}$ ) seem to be involved in the control of basal tension and membrane potential.<sup>94</sup> These channels may be possible targets for new drugs aimed at the treatment of bladder overactivity.

The first generation of ATP-sensitive potassium channel openers, such as cromakalim and pinacidil, were found to be approximately 8 to 200 times more potent as inhibitors of vascular than of detrusor smooth muscle.<sup>95,96</sup> This lack of selectivity is reflected also in the clinical trials performed with these drugs, where no bladder effects have been found at doses that lower blood pressure.<sup>97,98</sup> However, new drugs with  $K_{ATP}$ -channel-opening properties have been described that may be useful for treatment of bladder overactivity.<sup>99,100</sup> Zeneca ZD6169 and its analogs were shown to activate  $K_{ATP}$  channels in guinea pig detrusor strips as well as in human bladder cells.<sup>101,102</sup> ZD6169, given orally, was claimed to have an *in vivo* selectivity, significantly reducing micturition frequency in rats at doses that produced no cardiovascular effects.<sup>99</sup> Because selectivity for bladder tissue was not obvious *in vitro*,<sup>96</sup> the mechanism of the claimed bladder selectivity is unclear. Yu *et al.*,<sup>105</sup> giving ZD6169 intravesically, found the drug to increase the intercontraction interval in normal, but not in capsaicin-treated, rats. *C-fos* gene expression in the spinal cord, induced by acetic acid instilled into the bladder, was suppressed by pre-

treatment with intravesical ZD6169. The authors concluded that intravesical ZD6169 can influence bladder capacity by suppressing capsaicin-sensitive C-fiber afferents in the bladder. This may also be the case when the drug is given by other modes of administration.

Potassium channel opening is an attractive way of treating bladder overactivity because it would make it possible to eliminate undesired bladder contractions without affecting normal micturition. If the bladder effects of, for example, ZD6169 can be demonstrated in humans without exerting any cardiovascular actions, the principle of potassium-channel opening may represent a promising way of treating bladder overactivity.

**Phosphodiesterases.** Phosphodiesterases (PDEs) regulating intracellular cyclic nucleotide metabolism may influence contraction and relaxation of detrusor smooth muscle. In both porcine<sup>104</sup> and human<sup>105,106</sup> detrusor, several PDE isoenzyme families exist. Kinetic characteristics, together with functional *in vitro* studies, suggest that PDE I may be of importance in the intracellular regulation of human detrusor tone. The PDE I inhibitor vinpocetine was more effective than other selective PDE inhibitors in relaxing carbachol-contracted detrusor strips.<sup>106</sup> Initial experiments with vinpocetine in patients with urge incontinence and low-compliance bladder were promising,<sup>107</sup> but whether this means that vinpocetine or any other selective inhibitor of PDE I will be useful in the treatment of bladder overactivity remains to be established in controlled clinical trials.

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